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Research Article

To study the role of transdermal nitroglycerine (tNTG) in enhancing the effect of low dose intrathecal neostigmine on post-operative analgesia in patients undergoing lower abdominal and lower limb surgery under spinal anesthesia with bupivacaine.

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Abstract: Despite advances in the treatment of postoperative pain, many patients still suffer from pain after surgery, probably due to difficulties in balancing an effective postoperative pain treatment regimen with acceptable side effects. Intrathecal analgesia with a variety of drugs is a widely accepted practice for the treatment of both acute and chronic pain. The purpose of this study was to determine whether association of transdermal nitroglycerine would enhance analgesia from a low dose of intrathecal neostigmine in patients undergoing lower abdominal and lower limb surgery during spinal anesthesia with bupivacaine. 120 patients undergoing lower limb or lower abdominal surgery under spinal anaesthesia were randomly divided into four groups to receive hyperbaric bupivacaine alone or with intrathecal neostigmine and /or transdermal nitroglycerine. After the conclusion of surgery, pain was assessed for 24 hours postoperatively with the help of Linear Visual Analogue scale. At the end of 24 hrs, patients were evaluated for average VAS score, time since spinal anaesthesia to first dose of rescue analgesic and total dose of analgesic required. Side effects complained by the patients were recorded throughout the study period. In results Low dose intrathecal neostigmine enhances the postoperative analgesia of intrathecal bupivacaine. This analgesia is greatly increased by application of transdermal nitroglycerine patch without any significant increase in incidence of side effects.
Keywords: Bupivacaine, Neostigmine, Transdermal Nitroglycerine (tNTG), VAS Score, Postoperative analgesia

INTRODUCTION

Adequate control of the postoperative pain is very important, taking into account the fact that, beyond the fear for the outcome of surgery, the main concern of patients is related to postoperative pain's intensity. The inadequate relief of postoperative pain causes adverse physiologic effects and contributes to significant morbidity and mortality, resulting in the delay of patient recovery and return to daily activities [1]. Because aggressive treatment of acute postoperative pain is considered to be so beneficial, the Joint Commission on Accreditation of Healthcare Organizations has declared that "pain is the fifth vital sign"[2].

Despite advances in the treatment of postoperative pain, many patients still suffer from pain after surgery, probably due to difficulties in balancing an effective postoperative pain treatment regimen with acceptable side effects [3]. Intrathecal analgesia with a variety of drugs is a widely accepted practice for the treatment of both acute and chronic pain. Rathmell et al have thoroughly reviewed the role of intrathecal analgesia for acute pain. Opioid analgesics are the most commonly administered drugs for this purpose. Local anesthetics may also be used but in general are not as effective as combination of local anesthetics and opioids. Other useful analgesic additives include the α2-agonists, NSAIDs, NMDA receptor antagonists, acetyl cholinesterase inhibitors, adenosine, epinephrine and benzodiazepines [4].

Neostigmine is a para sympathomimetic agent that has been recently investigated for intrathecal, epidural, caudal and intra-articular routes of administration, as well as the addition of neostigmine to local anaesthetics for brachial plexus block and intravenous regional anaesthesia [5]. Postoperative analgesic effect of intrathecal neostigmine was first

reported by Hood DD in 1995 and represents a novel approach to providing analgesia. Neostigmine inhibits breakdown of an endogenous spinal neurotransmitter-acetylcholine, which has been shown to cause analgesia. Because acetylcholine has actions at other spinal sites (inhibition of motoneuron activity, excitation of sympathetic outflow), the degree to which analgesia and these side effects can be separated after spinal neostigmine administration will depend on the amount of tonic release of acetylcholine at each of these sites [6]. Intrathecal neostigmine produces some analgesia alone, but with a long delay and accompanied dose dependent side effects. For these reasons, neostigmine is most commonly combined with other agents.

Experimental data also suggest that the production of endogenous nitric oxide is necessary for tonic cholinergic inhibition of spinal pain transmission [7]. Nitroglycerine, a coronary vasodilator, with antihypertensive properties, is most commonly used for anginal pain, however studies have been recently published showing its analgesic activity for non-anginal pain. The addition of nitroglycerine to lidocaine for intravenous regional anesthesia improved sensory and motor block, reduced tourniquet pain and provided better postoperative analgesia than lidocaine alone. Systemic nitroglycerine administration was found to be a useful addition to spinal anesthesia. Postoperatively, visual analogue scale scores were lowered and the need for other analgesic medications was reduced when nitroglycerine patches were administered in addition to spinal ketamine, spinal neostigmine and spinal sufentanil [8,9,10]. Nitroglycerine (NTG) is metabolized to nitric oxide in the cell. Nitric oxide causes an increase in the intracellular concentration of cyclic guanosine monophosphate, which produces pain modulation in the central and peripheral nervous system [9]. Intrathecal neostigmine causes analgesia by inhibiting the breakdown of acetylcholine and experimental data suggest that the production of endogenous nitric oxide is necessary for tonic cholinergic inhibition of spinal pain transmission.

The purpose of this study was to determine whether association of transdermal nitroglycerine would enhance analgesia from a low dose of intrathecal neostigmine in patients undergoing lower abdominal and lower limb surgery during spinal anesthesia with bupivacaine.

MATERIAL AND METHODS

After obtaining approval of the Institutional Ethics Committee, 120 patients of ASA Grade 1 and 2, aged between 18 to 60 years, of either sex, scheduled for elective lower abdominal and lower limb surgeries were taken up for this prospective, randomized, double blind study and an informed consent was obtained from all the patients. A pre-anesthetic check-up was done a day before surgery and included a detailed history, a thorough physical and systemic examination.

Exclusion criteria included patients with any contraindication to spinal anaesthesia, ASA grade 3 or more, history of allergy to any of the used drug, patients with any cardiac disease, chronic headache, backache or any neurological deficit. Linear visual analogue scale was explained to all patients. In the pre-anaesthesia room, an intravenous line was secured using 18G cannula and patients were premedicated with midazolam 0.03 mg/kg IV and preloaded with crystalloid (R.L) 10 ml/kg, fifteen minutes prior to subarachnoid block. Using computer generated random numbers; patients were allocated to one of the following study groups;

- Group 1: or Control Group (CG) - Patients in this group received 3ml (15mg) of hyperbaric bupivacaine (0.5%) plus 0.5ml isotonic saline with transdermal placebo patch.
- Group 2: or Neostigmine Group (NG) - Patients in this group received 3ml (15mg) of hyperbaric bupivacaine (0.5%) plus 10mcg neostigmine in 0.5ml of isotonic saline and transdermal placebo patch.
- Group 3: or Transdermal Nitroglycerine Group (tNG) - Patients in this group received 3ml (15mg) of hyperbaric bupivacaine (0.5%) plus 0.5ml isotonic saline and transdermal nitroglycerine patch (5mg/24 hours).
- Group 4: or Combination Group (tN/NG) - Patients in this group received 3ml (15mg) of hyperbaric bupivacaine (0.5%) plus 10 mcg neostigmine in 0.5ml of isotonic saline and transdermal nitroglycerine patch (5mg/24 hours).

In the OT, monitors were attached and baseline vitals (HR, BP & SPO2) recorded. Under all aseptic precautions lumbar puncture was performed in sitting position at L3-L4 level, with 25 gauge spinal needle and 3.5ml of the drug solution was injected intrathecally over 30 seconds as per the group allocation. The patients were placed in supine position immediately after spinal injection on a flat table. The transdermal patch (placebo or nitroglycerine) was applied on the thorax (midsternum, T2-T4) 20 minutes after spinal puncture.

Vital parameters like heart rate, B.P (mean), respiratory rate, oxygen saturation and any change in ECG were recorded at 0, 2, 5 & 10 minutes after the subarachnoid block followed by ten minute interval till the end of surgery. Side effects like hypotension (MAP lower than 20% of baseline value) was treated by intravenous fluids and incremental doses of inj. mephentermine 6mg i/v and bradycardia (HR less

than 20% of the baseline) during surgery was managed by inj. atropine 0.3 mg i/v in incremental doses. Other side effects if any were managed accordingly.

After the conclusion of surgery, pain was assessed with the help of Linear Visual Analogue scale using a 10 cm line (0 – no pain: 10 – worst possible pain) at 0, 2, 4, 6, 8, 10, 12, 18 & 24 hrs postoperatively. Any patient with VAS score of more than 3 qualified for rescue analgesic (Inj. diclofenac 1.25 mg/kg i/m). Vital parameters and complications (like nausea, vomiting, hypotension, bradycardia, sweating and palpitation) were also recorded and appropriate treatment was provided to the patient.

At the end of 24 hrs, patients were evaluated for time since spinal anaesthesia to first dose of rescue analgesic and total dose of analgesic required by the patients. Side effects complained by the patient were recorded throughout the study period and appropriate treatment was provided to the patients.

RESULTS

At the end of study data collected was compiled and analyzed statistically using Pearson Chi-Square test to compare non-parametric data and ANOVA with Post Hoc Tukey test for parametric data. P-value less than 0.05 were considered to be statistically significant.

In our study there was no statistically significant (P>0.05) difference among all four groups in terms of demographic data, type and duration of surgery. Although the sex distribution of patients between four groups was statistically insignificant, females constituted majority of patients because of the higher inclusion of surgical procedures like hysterectomies in our study [Table 1].

Table 1: Demographic Data

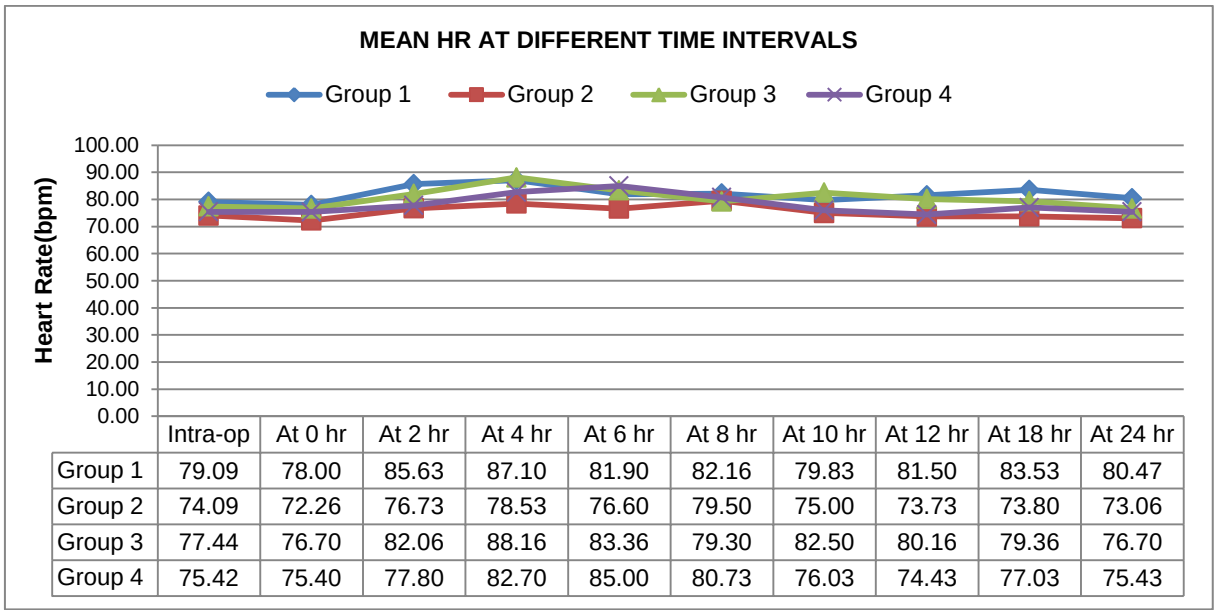
Parameter	G1	G2	G3	G4	F value	P value
ASA Class ½	18/12	19/11	20/10	17/13		
Sex (M/F)	8/22	9/21	8/22	10/20		
Mean Age (yrs)	43.23 ±10.51	46.07 ± 10.30	44.43 ± 11.18	46.13 ± 11.97	0.483	0.694^{NS}
Mean Weight (Kgs)	63.56s ± 9.66	59.13 ± 7.61	61.50 ± 7.56	62.16 ± 7.79	1.527	0.211^{NS}
Duration of Surgery (min)	85.33 ± 22.08	93.16 ± 21.95	87.66 ± 19.72	91.00 ± 22.02	0.786	0.504^{NS}

Intraoperatively there were clinically insignificant differences in mean heart rate of the four groups; 79.09bpm (CG), 74.09bpm (NG), 77.44bpm (tNG) and 75.42bpm (tN/NG). The intraoperative mean systolic pressures in study groups was 122.61mmHg (CG), 122.04mmHg (NG), 118.46mmHg (tNG) and 116.30mmHg (tN/NG) (P=0.001). The intraoperative mean diastolic pressure in the study groups was 78.72mmHg (CG), 76.57mmHg (NG), 75.02mmHg (tNG) and 73.87mmHg (tN/NG) (P=0.001). The difference in the intraoperative mean arterial pressures (mean) amongst the four groups was also statistically significant (P=0.004). The MAP (mean) recorded was 93.46mmHg (CG), 91.80mmHg (NG), 89.47mmHg (tNG) and 88.90 mmHg (tN/NG). Although statistically significant differences were seen in average blood pressure readings (SBP, DBP, MAP), all these differences were clinically insignificant and did not warrant any additional intervention in any group. Our study recorded lower intraoperative respiratory rates in neostigmine group (16.82bpm) and combination group (17.25bpm) as compared to control group (18.24bpm) and transdermal nitroglycerine group (18.05bpm). However no incidence of respiratory depression was noted in any of the groups. The difference was statistically significant amongst the groups (P<0.001). Mean oxygen saturation (SPO2) in the four groups was 99.55% (CG), 99.59% (NG), 99.72% (tNG) and 99.63% (tN/NG). The difference was clinically and statistically insignificant (P=0.734) [Table 2].

Table 2: Intraoperative Parameters

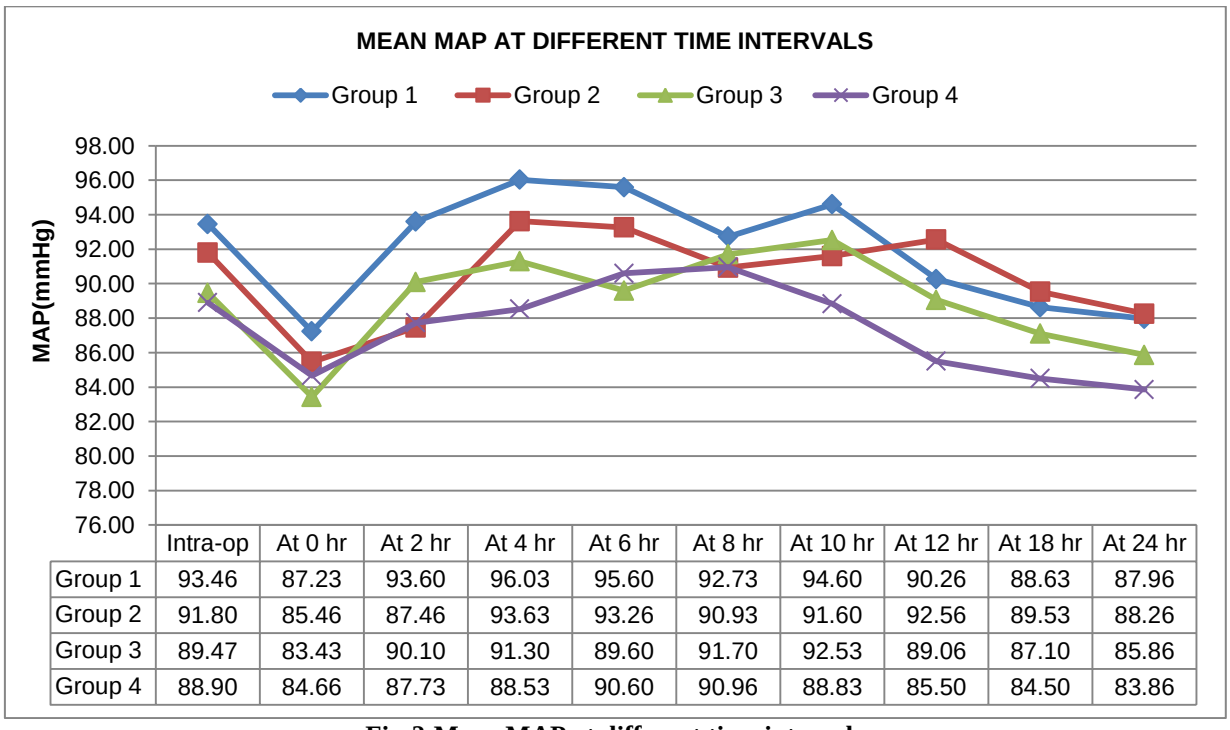
Vital Parameter	Mean Values ± SD				F value	P value
	Group 1	Group 2	Group 3	Group 4		
HR	79.09 ± 6.79	74.09 ± 9.51	77.44 ± 6.49	75.42 ± 7.25	2.519	0.061^{NS}
SBP	122.61 ± 6.17	122.04 ± 8.66	118.46 ± 5.94	116.30 ± 6.71	5.570	0.001*
DBP	78.72 ± 4.78	76.57 ± 5.53	75.02 ± 4.55	73.87 ± 4.31	5.687	0.001*
MAP	93.46 ± 5.16	91.80 ± 6.47	89.47± 4.83	88.90 ± 4.71	4.693	0.004*
RR	18.24 ± 1.05	16.82 ± 1.36	18.05 ± 1.12	17.25 ± 1.15	10.060	<0.001**
SPO2	99.55 ± 0.65	99.59 ± 0.68	99.72 ± 0.49	99.63 ± 0.56	0.428	0.734^{NS}

Post-operatively mean heart rates were lower in the neostigmine group (NG) and combination group (tN/NG) as compared with the other two groups [FIG 1]. The mean MAPs recorded at different time intervals were consistently lower in patients with transdermal nitroglycerine patch applied on ventral thorax (tNG and tN/NG). Although no treatment was needed for hypotension by any of patient in the two groups, the statistically significant low MAPs in these two groups of patients was probably because of sustained plasma NTG concentration [FIG 2]. Also the Group2 (NG) and Group4 (tN/NG) had lower respiratory rates recorded at different time intervals. The higher respiratory rates in Group1 (CG) and Group3 (tNG) probably reflect pain as evidenced by the higher VAS scores [FIG 3]. Postoperatively also the SPO2 recorded at different time intervals was clinically and statistically insignificant [FIG 4].



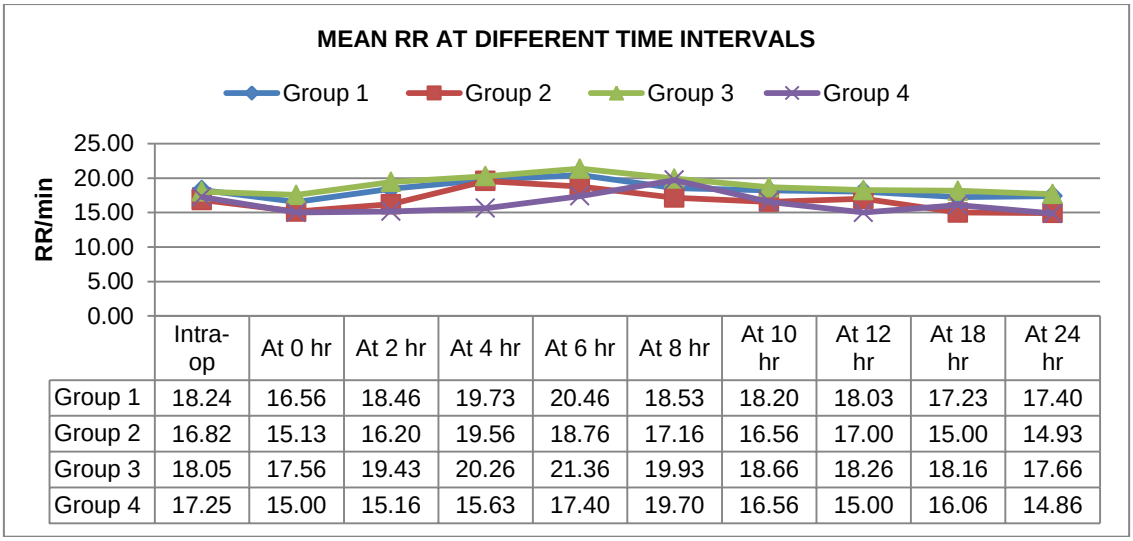
	Intra-op	At 0 hr	At 2 hr	At 4 hr	At 6 hr	At 8 hr	At 10 hr	At 12 hr	At 18 hr	At 24 hr
Group 1	79.09	78.00	85.63	87.10	81.90	82.16	79.83	81.50	83.53	80.47
Group 2	74.09	72.26	76.73	78.53	76.60	79.50	75.00	73.73	73.80	73.06
Group 3	77.44	76.70	82.06	88.16	83.36	79.30	82.50	80.16	79.36	76.70
Group 4	75.42	75.40	77.80	82.70	85.00	80.73	76.03	74.43	77.03	75.43

Fig-1: Mean HR at different time intervals



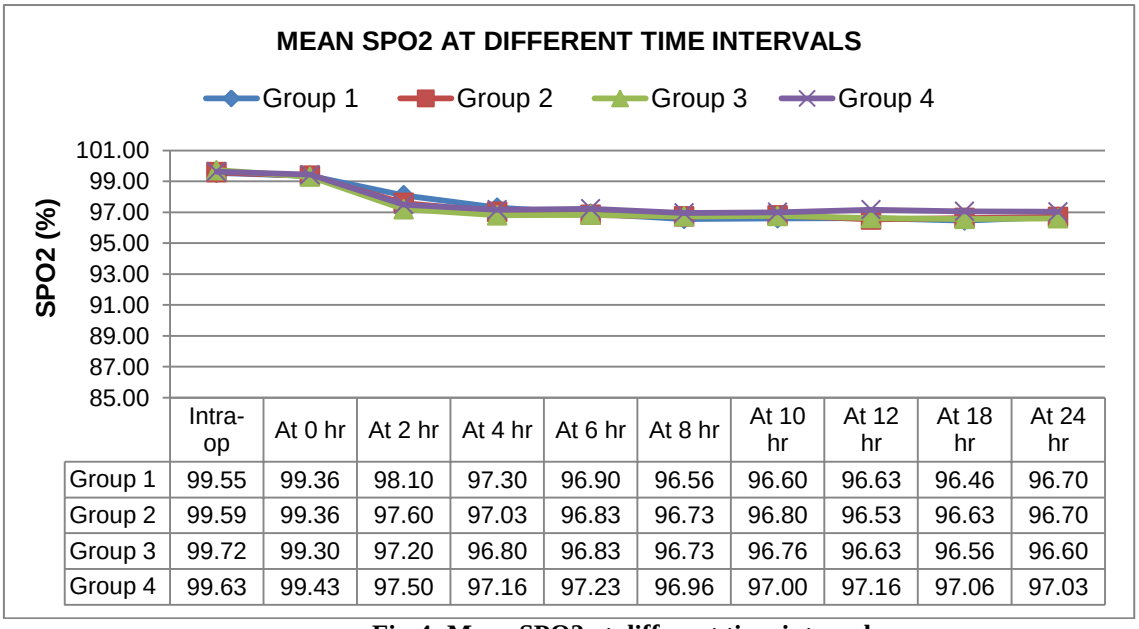
	Intra-op	At 0 hr	At 2 hr	At 4 hr	At 6 hr	At 8 hr	At 10 hr	At 12 hr	At 18 hr	At 24 hr
Group 1	93.46	87.23	93.60	96.03	95.60	92.73	94.60	90.26	88.63	87.96
Group 2	91.80	85.46	87.46	93.63	93.26	90.93	91.60	92.56	89.53	88.26
Group 3	89.47	83.43	90.10	91.30	89.60	91.70	92.53	89.06	87.10	85.86
Group 4	88.90	84.66	87.73	88.53	90.60	90.96	88.83	85.50	84.50	83.86

Fig-2:Mean MAP at different time intervals



	Intra-op	At 0 hr	At 2 hr	At 4 hr	At 6 hr	At 8 hr	At 10 hr	At 12 hr	At 18 hr	At 24 hr
Group 1	18.24	16.56	18.46	19.73	20.46	18.53	18.20	18.03	17.23	17.40
Group 2	16.82	15.13	16.20	19.56	18.76	17.16	16.56	17.00	15.00	14.93
Group 3	18.05	17.56	19.43	20.26	21.36	19.93	18.66	18.26	18.16	17.66
Group 4	17.25	15.00	15.16	15.63	17.40	19.70	16.56	15.00	16.06	14.86

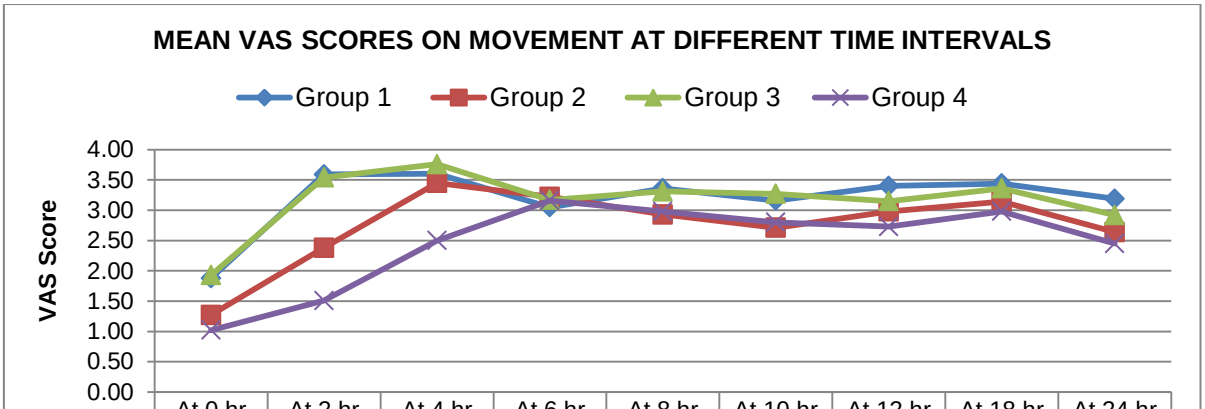
Fig-3: Mean RR at different time intervals



	Intra-op	At 0 hr	At 2 hr	At 4 hr	At 6 hr	At 8 hr	At 10 hr	At 12 hr	At 18 hr	At 24 hr
Group 1	99.55	99.36	98.10	97.30	96.90	96.56	96.60	96.63	96.46	96.70
Group 2	99.59	99.36	97.60	97.03	96.83	96.73	96.80	96.53	96.63	96.70
Group 3	99.72	99.30	97.20	96.80	96.83	96.73	96.76	96.63	96.56	96.60
Group 4	99.63	99.43	97.50	97.16	97.23	96.96	97.00	97.16	97.06	97.03

Fig-4: Mean SPO2 at different time intervals

Mean computed visual analogue scores on movement over 24 hrs in the four groups were 2.91 (CG), 2.50 (NG), 2.78 (tNG) and 2.15 (tN/NG). On comparing the mean VAS scores recorded over different time intervals, it was seen that VAS scores in group1 or control group (CG) and group3 or transdermal nitroglycerine group (tNG) were comparable and persistently greater than that of group2 or neostigmine group (NG) and group4 or combination group (tN/NG). Also the average VAS scores of combination group were significantly lower than neostigmine group [Fig 5].



	At 0 hr	At 2 hr	At 4 hr	At 6 hr	At 8 hr	At 10 hr	At 12 hr	At 18 hr	At 24 hr
Group 1	1.88	3.59	3.60	3.05	3.36	3.16	3.40	3.44	3.19
Group 2	1.27	2.38	3.45	3.22	2.93	2.71	2.98	3.14	2.64
Group 3	1.93	3.54	3.76	3.17	3.31	3.27	3.15	3.36	2.92
Group 4	1.02	1.51	2.50	3.16	2.98	2.80	2.73	2.98	2.45

Fig-5: Mean VAS scores on movement at different time intervals

The mean duration of analgesia was 198.66 minutes, 337.33 minutes and 203.16 minutes in the control group (CG), neostigmine group (NG) and transdermal nitroglycerine group (tNG) respectively while the mean duration of analgesia in the combination group (tN/NG) was 488.39 minutes. The difference was clinically and statistically highly significant (P<0.001). However there was no significant (P>0.05) increase in duration of analgesia between group1 (CG) and group3 (tNG) [Table 3].

Table 3: Time to First Analgesic

Group	Range	Mean (Time in min)	F value	P value
Group 1	145 – 250	198.66 ± 25.76	99.946	< 0.001**
Group 2	240 – 480	337.33 ± 62.01		
Group 3	140 – 290	203.16 ± 36.04		
Group 4	230 – 840	488.39 ± 128.91		

** p < 0.001; Highly significant

The number of rescue analgesics required as a measure of number of analgesic injections per patient was 73 (control group), 59 (neostigmine group), 71 (transdermal nitroglycerine group) and 44 (combination group) in the respective groups. All the patients in first three groups needed rescue analgesic at some point of time within the first 24hrs while as two patients from group4 (combination group) did not need rescue analgesia at all. The mean consumption of rescue analgesic per patient among study groups was 2.43 (CG), 1.97 (NG), 2.36 (tNG) and 1.46 (tN/NG). This difference again was clinically and statistically highly significant (P<0.001) with the combination group requiring the least amount of analgesic injections per patient followed by neostigmine group [Table 4].

Table 4: Rescue Analgesics Required

Group	Total Number of Rescue analgesics Reqd.	Range	Mean ± STD	F value	P value
Group 1	73	1 – 4	2.43 0.72	12.585	< 0.001**
Group 2	59	1 – 3	1.97 0.66		
Group 3	71	1 – 3	2.36 0.61		
Group 4	44	0 – 3	1.46 0.73		

** p < 0.001; Highly significant

DISCUSSION

Despite advances in treatment of postoperative pain many patients still suffer from pain after surgery probably due to difficulties in balancing an effective postoperative treatment regime with acceptable side effects [3]. Postoperative pain management relies heavily on pharmacological interventions. The pharmacological control of pain can be classified

according to three main drug classes viz (i) Local anesthetics (ii) Opioids and (iii) Non steroidal anti-inflammatory drugs (NSAIDs) and the various ways in which they may be combined.

The results of this study show a significant increase in postoperative analgesia when neostigmine is added to intrathecal bupivacaine. Neostigmine-induced augmentation of analgesia, when supplemented to bupivacaine, has been shown in other studies [3, 11, 12]. Analgesic effect of intrathecal neostigmine is secondary to acetylcholine release in the spinal cord tissue [13]. During surgical stimuli, a pre-existent spinal cholinergic tonus is activated. Neostigmine, an anticholinsterase drug increases the concentration of acetylcholine in the cerebrospinal fluid and acetylcholine bioavailability at the cholinergic nerves within the spinal cord. Elevated acetylcholine due to the surgical stimulus and also acetylcholine preserved from cholinesterase activity after intrathecal neostigmine, binds to muscarinic and nicotinic nerve terminals in the spinal cord [14].

Electrophysiological studies have demonstrated that cholinergic receptor agonists produce inhibitory effects on spinal dorsal horn neurons, including spinothalamic tract neurons [15]. This suggests that a spinal cholinergic system plays an important inhibitory role in the modulation of nocioceptive transmission.

Since nitric oxide (NO) was shown to be a central neurotransmitter, there have been several reports of the relationship between NO and pain processing in the brain and the spinal cord [16]. Acetylcholine and morphine induce analgesia via activation of the arginine-NO-cGMP pathway [17]. Guanylate cyclise activity in the brain is markedly stimulated by NO, generated from L-arginine or provided through an exogenous source as in the present study through transdermal nitroglycerine. Evidence exists that NO modulates the synaptic transfer of signals in both the central and the peripheral nervous system. The transdermal nitroglycerine patch has been related to NO formation during degradation of organic nitrates. A current study also provides evidence that acetylcholine stimulate nitric oxide synthesis in the spinal cord and this synthesis is necessary for the expression of analgesia secondary to the cholinomimetic agent such as spinal neostigmine [18].

In our study we did not find any major complication attributable to the use of neostigmine or transdermal NTG. Side effects commonly noted were nausea, hypotension, bradycardia and vomiting and there was statistically no significant difference in occurrence of side effects between the four groups [Fig 6].

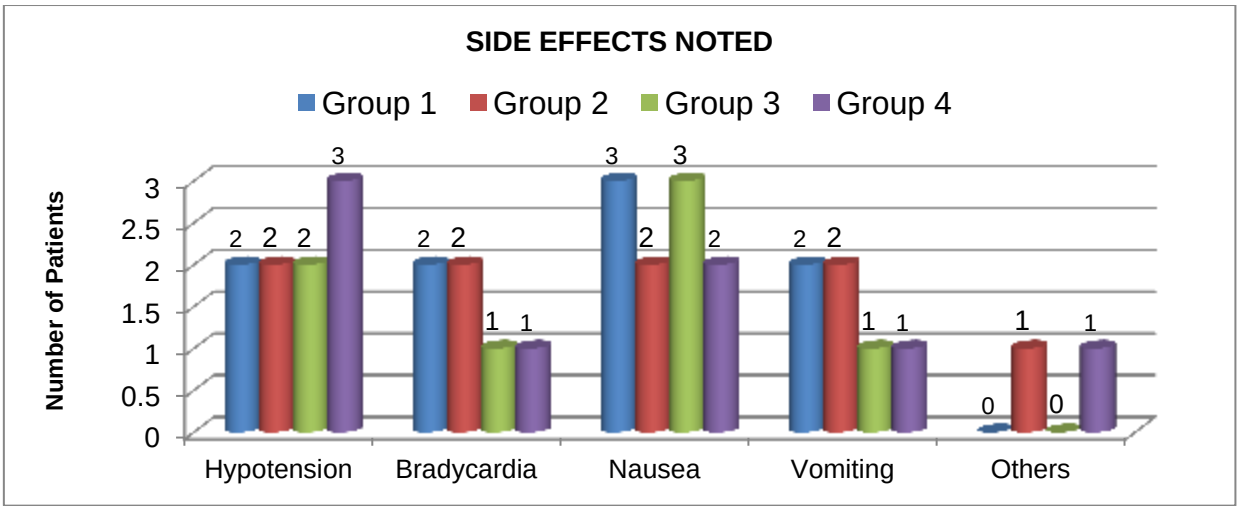


Fig-6: Side Effects Noted

One patient each in the neostigmine group (NG) and nitroglycerine-neostigmine group (tN/NG) reported sweating with palpitations which in both the cases did not require any treatment and was managed with simple reassurance and mild sedation. Our study did not match the studies of Ho KM et al who reported increased incidence of nausea, vomiting, and bradycardia with intrathecal neostigmine [19]. The low incidence of side effects in our study is probably because of low dose (10mcg) of neostigmine used which is again in accordance with the work of Hood et al who reported incidence and severity of adverse events from intrathecal neostigmine to be dose related[6].

Further, the present study showed that the combination of 5 mg/day transdermal nitroglycerine patch and intrathecal low dose neostigmine (10 mcg)

resulted in an average of more than 8 hours of postoperative analgesia after bupivacaine spinal block, compared to 3.25 hours in the control group. The combination increased the duration of analgesia, as the first requirement of rescue analgesia was delayed by appx.5 hours in this group compared from the control group. In similar studies [7, 12, 20] including that of ours, it was observed that intrathecal neostigmine along with transdermal nitroglycerine patch provided longer duration of analgesia following bupivacaine spinal block and significantly minimized the analgesic consumption as compared to only intrathecal bupivacaine. Hence we conclude that combination of transdermal nitroglycerine with low dose intrathecal neostigmine and bupivacaine significantly enhances the postoperative analgesia without concurrent increase in side effects and the combination provides a safe and effective alternative to other modalities of postoperative pain management.

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